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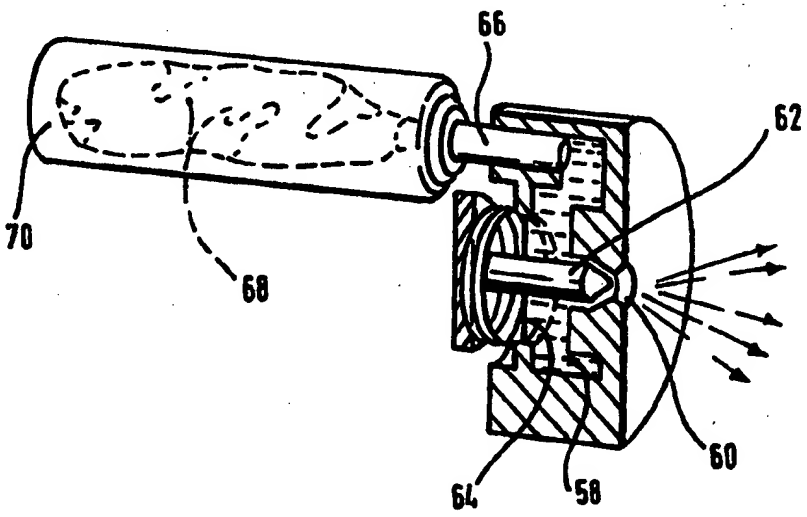
(54) Title: OCULAR TREATMENT DEVICE

(57) Abstract

An ocular treatment device and methods for applying a treatment liquid to the eye are disclosed. The invention provides for the discharge of treatment liquid from a nozzle (60) in a jet or multiple droplets of at least 20 μm diameter to a target area of the eye. They are discharged at a speed sufficient to ensure that they are carried to the target area of the eye under their own momentum. Provision is made for the total quantity of treatment liquid discharged to be predetermined corresponding to a specific dosage form, and for this purpose a separate volume of the liquid may be drawn from a reservoir prior to discharge. In another arrangement, treatment liquid in a reservoir (68) is under continuous pressure, and the amount of liquid discharged is determined by the operation of a discharge valve (62).



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OCULAR TREATMENT DEVICE

This invention relates to ocular treatment devices, and particularly to a device of the kind which is operable to deliver to the eye treatment fluids in the form of jets and droplets. Such a device is disclosed in European Patent Specification No. 0224352. The device of that specification generates a stream of electrically charged droplets, which is directed towards the earthed target site by means of an electrical field. While this is suitable for a certain range of liquids there are potential disadvantages in the delivery of charged droplets to sensitive treatment areas such as the eye where adverse reactions could be provoked.

The present invention is directed at an ocular treatment device which can direct small uncharged droplets or jets of fluid towards a target area in the eye. A device according to the invention comprises a reservoir for a source of treatment liquid, the reservoir being coupled to a discharge nozzle; means for pressurising treatment liquid from the reservoir, and providing for discharge of such pressurised liquid from the nozzle in multiple droplets having a minimum diameter of about 20 μm diameter to a target area of the eye. In an alternative, the device may be adapted to discharge a jet or jets of fluid with a minimum diameter of typically about 10 μm. If such a 10 μm jet is broken up, the result will be droplets of around 20 μm diameter. In Rayleigh atomisation the droplets diameter is 1.89 times the jet diameter. Thus, the invention also includes devices adapted to generate a jet or jets of treatment fluid, and break it or them up to discharge droplets of diameters of 20 μm or more.

The invention also provides a method of applying a treatment liquid to the eye comprising pressurising a treatment liquid from a reservoir, and discharging such liquid from a nozzle in a jet or jets of minimum

diameter 10 μm or in multiple droplets of at least 20 μm diameter to a target area of the eye at sufficient speed to reach said target area under their own momentum.

The invention uses a physical mechanism for creating the droplets, or at least a mechanism that does not result in the droplets carrying an electrical or electromagnetic charge, and for this purpose can use means similar to those already used in the ink jet printing industry. A few such techniques such as piezoelectric, bubble jet, and dry jet, are suitable, although other techniques could certainly be considered. Some will generate droplets from a source, and immediately direct them to the target area. Others will use an intermediate chamber or component which will receive and discharge jets or droplets either singly or simultaneously. For example, a collapsible chamber can be maintained loaded with treatment liquid from a source, and completely emptied and discharged towards the target area as required. A dosage unit can be used to control the jets or the number or amcunt of droplets created and directed to the target area.

By using a physical mechanism for generating the jets or droplets, there is little if any restriction on the nature of the liquid from which they are to be formed. Thus, aqueous or non-aqueous liquids can be used. Aqueous liquids are generally unsuited for use in electrodynamic systems, or in systems requiring the droplets to be created by means of an electrostatic charge. Particularly as for ocular treatment many of the liquids used are in aqueous solution, this feature of the invention is of particular benefit. Uncharged jets or droplets can also be easier to control as adverse effects from humidity and other ambient conditions are less relevant.

The generating means can provide the seriatim or linear delivery of droplets from a single orifice or the simultaneous delivery of droplets through a plurality of

orifices. The nature of the treatment required will determine what form of delivery is appropriate, but a single orifice will normally be appropriate where the treatment is to focus on a particular area of the eye, whereas a multi-orifice system can be used if a more general or "blanket" distribution is appropriate. The use of a multi-orifice has a particular advantage in that it can provide the simultaneous delivery of different treatment liquids. This can be additionally beneficial as one orifice can be used to deliver a stimulant, the arrival of which at the eye surface will be recognised by the user, therefore confirming that the treatment dose as a whole has reached its target. Such a stimulant is preferably a coolant, as there is normally a ready recognition of a sharp lowering of a temperature at the eye surface.

Other features can also be employed in devices according to the invention to indicate the successful delivery of a treatment fluid to its target. A light can be provided to maintain the eye open, and this could typically be white. Alternatively, a coloured system may be employed in which a different colour indicates the stage of treatment. For example, the device can be offered up to the eye showing a red light, which will switch to green only after the predetermined dose has been dispatched.

As noted above, the invention avoids the use of charged droplets, and additional steps can be taken to ensure that they do not acquire some electrostatic charge unintentionally. For example, the entire device or the liquid reservoir from which the jets or droplets are generated can be earthed, or an earthing shroud can be disposed downstream of a discharge nozzle or nozzle matrix. It is also possible to include a sterilising unit in the device close to the discharge nozzle or nozzle matrix, or even an on-line filter with a 0.22μm filter to ensure sterility at the point of discharge.

The provision of these features can obviate the need to use any kind of preservative in the liquid source. It is established that even very small quantities of preservatives can provoke an adverse reaction when used in ocular treatment, and any means by which their use may be avoided can only be beneficial.

Pursuant to the above, the present invention is concerned primarily, but not exclusively, with multi-dose devices of the above type which minimise the risk of contamination of the treatment fluid held in a supply reservoir. This can be achieved by ensuring that a discharge valve from which fluid is released opens and closes only while the fluid upstream of the valve is under pressure. Additionally, the design of the valve itself may be made specifically to minimize the risk of contamination at the valve services and particularly to minimize the retention of fluid on surfaces on the downstream side of the valve.

In one embodiment of the invention, a reservoir of treatment fluid is confined in a flexible container, itself enclosed in a sealed housing with a pressurized atmosphere comprising a suitable propellant fluid. The reservoir is coupled to a pressure chamber in one wall of which the discharge valve is located. The discharge valve may be electrically or manually operated to release treatment fluid under the pressure at which it is maintained. This pressure is substantially constant as a consequence of the manner in which the reservoir is housed. Alternative means of maintaining the treatment fluid at a substantially constant pressure include the use of elastic container walls, fluid or other physical means of applying pressure thereto. Nevertheless, we have found that the use of a propellant fluid in a housing in which a sealed container providing the reservoir is disposed provides a reliable means of maintaining a substantially constant pressure in the fluid as the container is emptied.

The valve mechanisms used in some devices according to the invention have complementary conical and/or spherical surfaces which, when separated, allow fluid to pass along a path of circular cross-section. The valve mechanisms will preferably be designed to ensure that only a minimal portion, if any, of the valve mechanism is exposed externally, as well as to the treatment fluid in the treatment chamber. In one embodiment, the inner valve element is coupled to a valve stem sealed to a flexible diaphragm forming an opposite boundary of the pressure chamber. The valve stem can then be operated from outside to withdraw the inner element from the outer valve element and thereby release the pressurized fluid. In another embodiment, the inner valve element is resiliently held against the outer element, and the treatment fluid pressure is progressively increased until it is sufficient to separate the elements. This technique has the advantage of substantially predetermining the pressure of the fluid at the point of release, but precise control of the valve opening period is more difficult.

Discharge valves of the kind described above can be oriented with their conical surfaces facing towards or away from the pressure chamber. Where they face toward the pressure chamber, then a direct operating system is preferred. If the valve is to be actuated by fluid pressure, then it is preferred that the valve surfaces face away from the pressure chamber; i.e., towards the treatment target. In all embodiments of the invention, the discharge valve may be operated directly or indirectly by electric units such as a solenoid. This facilitates consistency of operation with respect both to discharge delivery pressure and duration of valve opening times.

Devices according to the invention can also include a number of safety features which are already well established in dosing devices of various kinds. The

reservoir of liquid in a device will of course have a finite capacity, and a dose recorder may be included to provide an indication of the number of doses remaining or delivered. A delay mechanism can also be included to prevent the inadvertent delivery of a multiple dose. In combination with the delivery signal features referred to above, this can be of significant benefit.

It will be recognised that devices according to the invention can be for personal or hand held use, or for use on a more regular basis in institutions. For whatever use, means can be provided for ensuring a proper spacing between the device and the eye to be targeted, and this can be made adjustable, particularly in the devices adapted for institutional use. In this respect, it will be noted that the jet and droplet generating mechanisms contemplated in the present invention will be well capable of discharging droplets substantially horizontally or vertically upwards over a minimum distance, thereby not requiring a user to arrange for the device to be operated from directly above an eye.

Embodiments of the invention will now be described by way of example and with reference to the accompanying schematic drawings wherein:

Figure 1 is a side elevation of an ocular treatment device in accordance with a first embodiment of the invention;

Figure 2 is an end view of the device of Figure 1 in the direction of arrow A;

Figure 3 shows a perspective view of a second embodiment of the invention;

Figure 4 shows a detail cross-section of the discharge valve and the device of Figure 3;

Figure 5 shows a perspective view of a third embodiment of the invention; and

Figure 6 is a detailed view showing the operation of the device of Figure 5; and

Figure 7 is a block diagram of a system in which the pumping system for the treatment fluid is spaced from the discharge orifice.

The treatment device shown in Figures 1 and 2 comprises a body 2 housing a dosage control unit with an operating button or switch 4. At the left hand end of the housing 2 as shown, is mounted a matrix of discharge nozzles which receive treatment liquid from a source 8. Extending from the housing 2 beyond the matrix 6 are two projections or mounts 10 for locating the device relative to a user's face in front of an eye to be treated. Power to generate and discharge jets and droplets from the matrix 6 is provided by a battery located in a pocket 12 at the opposite end of the housing 2.

As best shown in Figure 2, the matrix 6 comprises nine separate nozzles 14. Each nozzle 14 may be coupled to the source 8 via a chamber fitted with a piezoelectric transducer to discharge a droplet therefrom. The nozzle or nozzles to be activated in this way will be determined according to the dosage unit in the housing 2, and it will be appreciated that different manners of delivery may be selected. A single "blanket" dose may be delivered by simultaneously activating all nine nozzles. Alternatively, only the central nozzle may be activated to deliver a jet, one, or a sequence of droplets to substantially the same target area. Although as shown the source 8 provides only the source of a single treatment liquid, it can be divided such that different nozzles are fed with different liquids. Particularly, the peripheral eight nozzles might be used to deliver a blanket dose of treatment liquid, and the central nozzle to deliver a stimulant that will be recognised by the user when it contacts the eye, thereby informing the user that the treatment liquid has reached its target. Another

possible delivery signal mechanism uses a light source 16 which will show one colour say red, until the switch 4 is pressed, at which point it switches to another colour say green. Although a piezoelectric device has been referred to above as the activator for the nozzles 14 in the illustrated embodiment, it will be understood that other droplet generating mechanisms can be employed. Reference has already been made to bubble jet systems and dry jet systems. Another possible system is the continuous jet in which a stream of liquid spontaneously breaks into smaller droplets under appropriate stimulus. This system can be effective, but uses greater quantities of liquid than the others as normally a shutter system has to be used to control the dosage delivered.

Devices according to the invention can typically generate droplets with diameters of the order of 50 μm, enabling the delivery of multiple droplets in metered doses of very low volume, 5 μl being typical. However, much smaller droplets can be desirable in some applications, as can much larger droplets in others, a typical range being 20 to 200 μm. What is important though is that each droplet has sufficient mass to establish momentum to carry it to the target. In this respect devices of the invention are distinct from prior devices which generate sprays with little or no directed movement. A typical delivery velocity is 10 m/s, but other velocities may be appropriate in particular applications. Because of the manner in which the dose is delivered, by using a device according to the invention a much greater proportion of treatment liquid will actually make contact with the eye, leading to less wastage, reduced risk of systemic absorption and importantly, less flooding of the eye and risk of provoking blinking or watering which can result in a treatment being wasted.

As noted above, devices according to the invention

are adapted to discharge treatment liquid in multiple droplets in the range 20 to 200 μm diameter. In order to create a smooth discharge of liquid through the nozzle or nozzles, in the embodiment of Figures 1 and 2 the nozzles or openings preferably have a cross-section which tapers towards the discharge and, with the inlet diameter of the order of three times that of the outlet. The preferred axial length of the openings is 1 to 5 times the outlet diameter, and at the outlet the opening may be made substantially cylindrical. This arrangement provides for the deployment of valve mechanisms which operate against the nozzle walls from the inlet side as in the embodiment of Figures 3 and 4 described below.

While the embodiment of Figures 1 and 2 has been described in the context of the device comprising a single unit, it may take the form of a modular system in which the delivery mechanism and the treatment liquid source are provided separately, or at least independent of each other. A liquid source can then be selected, and coupled to a delivery mechanism as desired. This enables the same delivery mechanism to be used for different treatments. Such a device of the invention for institutional use can provide for such selection to be at least partially automated.

The device shown in Figure 3 comprises a main body 22 on which is mounted a reservoir in the form of a bulb 24 supported between two rings 26. Each ring 26 is fitted with a plate 28, 30, and these plates are connected by a cylinder 32 in which a discharge pressure chamber is defined. The pressure chamber is connected to the main reservoir only through a one way valve 34 disposed substantially centrally in the cylinder wall.

A discharge valve 36 is fitted in the plate 28 at the front or discharge end of the cylinder 32. A piston 38 is fitted in the cylinder 32, and this either extends or is coupled to a piston rod which extends through the plate 30 for connection to a dispensing mechanism 40.

When the mechanism is actuated, the piston 38 is moved from its rest position to the left of the one way valve 34 as shown, to pressurize fluid in the cylinder 32 against the discharge valve 36. In this embodiment, the valve 36 is adapted to open when the fluid pressure in the cylinder 32 below the piston exceeds the preset value. However, the discharge valve might also be operated in response to, for example, the piston passing a predetermined point in its path towards the valve.

A fluid pressure-actuated discharge valve 36 is illustrated in Figure 4. A venturi nozzle 42 is formed in the plate 28, with its downstream cross-section closed by a ball member 44. On the upstream side of the plate 28, within the cylinder 32, a support is mounted for a resilient tie 46. The tie 46 holds the ball member 44 in place against the downstream cone of the venturi nozzle 42, and the tie 46 and the support therefor define the preset pressure value that must be exceeded before treatment fluid issues from the valve. As will readily be understood, the amount of fluid discharged will be determined by the movement of the piston 38 and the level of the preset value which determines valve closure. As soon as the fluid pressure falls below the preset value, the ball member 44 will re-engage with the juxtaposed conical surface of the venturi nozzle, and until the respective surfaces are engaged, treatment fluid will continue to be discharged. As a consequence, there is a minimal risk of contamination of the treatment fluid remaining in the cylinder 32 and indeed the reservoir 54. It will be appreciated that the tie 46 and the support therefor on the plate 28 can be adjustable to vary the preset pressure value. Once the valve has closed, the piston 38 is withdrawn past the one way valve 34, enabling the cylinder to refill with fluid from the bulb 24.

While the resilient tie 46 and support therefor on the plate 28 will determine the closure of the valve 36,

the amount of fluid discharged will of course be determined by the stroke of the piston 38. The piston/cylinder are typically dimensioned, and the dispense mechanism designed to provide for the discharge of five microlitres in a single stroke, with the preset pressure value being reached just as the piston passes the one way valve 34. This minimises the build up of negative pressure in the fluid as the piston is withdrawn. A spring 48 can be provided behind the plate 30 to withdraw the piston 38. The piston is normally advanced by a dispense button or trigger 50 which can be coupled directly to the piston 38, or indirectly via electric unit such as a solenoid.

In the device of Figures 5 and 6 the treatment fluid is kept under the same pressure throughout. The components are mounted in the body 52, and comprise a reservoir 54 and a discharge housing 56. As is better shown in Figure 6, a discharge housing 56 defines a pressure chamber 58 with a discharge nozzle 60 formed in one wall thereof. The nozzle 60 is closed from inside the pressure chamber 58 by means of a valve element 62 which traverses the chamber and is sealingly mounted in a diaphragm 64 which closes the opposite wall of the pressure chamber 58.

The pressure chamber 58 is coupled directly to the treatment fluid reservoir 54 via a connecting union 66. The reservoir comprises a flexible container 68 within a sealed casing 70. The casing 70 is filled with a propellant fluid which maintains the container 68 under continuous substantially constant pressure. This pressure is in turn imparted to the treatment fluid within the container and as a consequence, the pressure of the treatment fluid in the container 68 and the pressure chamber 58 is maintained at a substantially constant level.

With the arrangement described above, the treatment fluid in the device of Figures 5 and 6 is an essentially

closed system. With the treatment fluid in this system being under substantially constant positive pressure, the operation of the device is relatively straightforward. As soon as the valve element 62 is withdrawn from the nozzle 60, then the pressure of the fluid causes it to discharge from the nozzle 60. Movement of the valve can be controlled manually, but a solenoid drive unit is preferably included, as this enables electronics to be used to pre-program the valve to be opened for specific fixed periods. The device 22 provide a positive delivery of unit doses according to prescribed requirements.

A particular advantage of the device shown in Figures 5 and 6 is that the treatment fluid reservoir can easily be replaced. The reservoir can be provided as a pressurised unit with a seal in the union 66 which is broken as it is inserted into the discharge housing 56. If the device is to be adapted for use with replaceable reservoirs, then the discharge housing 56 may of course be provided with a bleed valve for the pressure chamber 58.

Figure 7 shows in block diagram form, a multi-dose forced-flow. A Hamilton syringe 72 is coupled to a stepper motor 74, the two being mounted in the same module 76. The outward end of the syringe 72 is connected by means of Teflon tubing to a spray head 78 which includes a simple reservoir with a detachable cap 80 in which the discharge orifice is formed. Thus, activation of the stepper motor 74 will depress a piston in the syringe 72 and discharge a corresponding amount of fluid in the syringe 72 along the tubing. This will result in the treatment fluid in the spray head being pressurised, and as a consequence a jet or stream of droplets are discharged from the orifice.

The operation of the stepper motor 76 and syringe 72 are controlled by a programmable electronics module 82 such as a MC20 Indexer. The use of such an

electronics control module provides for very accurate control of the stepper motor, and therefore the amount of fluid discharged from the Hamilton syringe 72. The Hamilton syringe typically has a capacity of 2.5 ml, and the tubing connecting the spray head 78 to the syringe 72 is typically a short length of 0.8 mm bore Teflon tubing. The spray head 78 comprises a cylindrical stainless steel chamber onto which is screwed a small molybdenum disc with a central aperture of the required size, typically 100 μm.

A multi-dose forced flow device of the type described above with reference to Figure 7 with a 100 μm orifice has been used in tests in which a single 5 μl dose of isotonic 4% Pilocarpine hydrochloride (Pilocarpine HCl) solution is administered to the corneal surface of the left eye of each of 10 rabbits, with the rabbits right eyes remaining undosed. The animals selected for the study were allowed to acclimatise for 4 to 5 days prior to treatment, and were subjected to manual restraining for the 2 days prior to the study to condition them to the procedures involved in dosing. In conducting the study, the following machine settings were used.

- 100 μm nozzle diameter
- 5 μl dose volume
- 2.5 cm distance between nozzle tip and animal eye
- sprays targeted towards the centre of the cornea of the animal eye
- Flow rate of 100 μl/s

The miotic response (reduction in pupil diameter) at various intervals following the application of the pilocarpine HCl solution was monitored under constant illumination using video photography. The value of the pupil diameter of the left eye was expressed in proportion to the diameter of a fixed reference aperture situated at an equal distance from the video camera.

The actual diameter was then calculated from the known diameter of the reference aperture.

Table 1 shows the pupil diameter of the left eye at different intervals following application of the test dose.

TABLE 1: Pupil Diameter (mm) Following Application of 5 µl spray of 4% Pilocarpine HCl Using Optidyne spray Device (Mean of 10 Rabbits)

Measurement Timepoint

	Dose (0 min)	+15 min	+30 min	+45 min	+ 1 hr	+1.5 hr	+ 2 hr	+2.5 hr	+ 3 hr	+3.5 hr	+ 4 hr
Mean	7.4	6.2	6.3	6.3	6.6	6.9	7.1	7.3	7.4	7.6	7.7
S.D.*	0.7	0.7	0.7	0.6	0.7	0.6	0.7	0.6	0.8	0.7	0.7

* Standard Deviation

CLAIMS

1. An ocular treatment device comprising a reservoir for a source of treatment liquid, the reservoir being coupled to a discharge nozzle; means for pressurising treatment liquid from the reservoir, and providing for discharge of such pressurised liquid from the nozzle in the form of a jet or in multiple droplets of at least 20 μm diameter to a target area of the eye.

2. A device according to Claim 1 including means for controlling the discharge of pressurised liquid to determine the total quantity of treatment liquid in a specified discharge.

3. A device according to Claim 1 or Claim 2 wherein the pressurising means acts continuously on treatment liquid in the reservoir, the device including a valve operable selectively to open the path of liquid from the reservoir to the discharge nozzle.

4. A device according to Claim 3 wherein the reservoir comprises a flexible bag confined in a chamber containing fluid under pressure.

5. A device according to Claim 3 or Claim 4 wherein the valve comprises an operating rod traversing a discharge chamber, mounted in a diaphragm sealed to a wall of the chamber at one end, and having a valve element resiliently biased against a valve seat defining the discharge nozzle in an opposite wall of the chamber at the other end.

6. A device according to Claim 1 or Claim 2 wherein the discharge nozzle is disposed at the end of a pressure cylinder with a piston therein, the cylinder being selectively connected to the reservoir to receive

treatment fluid therefrom, which connection is closed during discharge of fluid through the nozzle.

7. A device according to Claim 6 wherein said connection comprises a valve which is open when the piston is in a withdrawn position, but closed as the piston moves forward therefrom urging treatment liquid toward and through the nozzle.

8. A device according to Claim 6 or Claim 7 wherein the reservoir surrounds the pressure cylinder.

9. A device according to Claim 6 wherein the reservoir forms a bulb around the pressure chamber.

10. A device according to any of Claims 6 to 9 wherein the discharge nozzle has a valve seat defined in the outer face of a respective wall of the pressure chamber, with a valve element resiliently biased thereagainst, activating pressure being sufficient to overcome said bias and discharge liquid from the nozzle.

11. A device according to any of Claims 6 to 9 including a discharge valve comprising an operating rod traversing a discharge chamber, mounted in a diaphragm sealed to a wall of the chamber at one end, and having a valve element resiliently biased against a valve seat defining the discharge nozzle in an opposite wall of the chamber at the other end.

12. A method of applying a treatment liquid to the eye comprising pressurising a treatment liquid from a reservoir, and discharging such liquid from a nozzle in the form of a jet or in multiple droplets of at least 20 μm diameter to a target area of the eye at sufficient speed to reach said target area under their own momentum.

13. A method according to Claim 12 wherein a predetermined amount of treatment liquid corresponding to a specified dosage is pressurised and discharged.

14. A method according to Claim 12 wherein a reservoir of treatment liquid is pressurised, and a predetermined amount of treatment liquid corresponding to a specified dosage is discharged.

15. A method according to Claim 14 wherein the predetermined amount of treatment liquid is set by the operation of a discharge valve.

16. A method according to Claim 15 defined by a separate chamber which receives treatment liquid from the reservoir and in which it is further pressurised and discharged.

17. A method according to Claim 16 wherein the chamber is the cylinder of a piston cylinder mechanism.

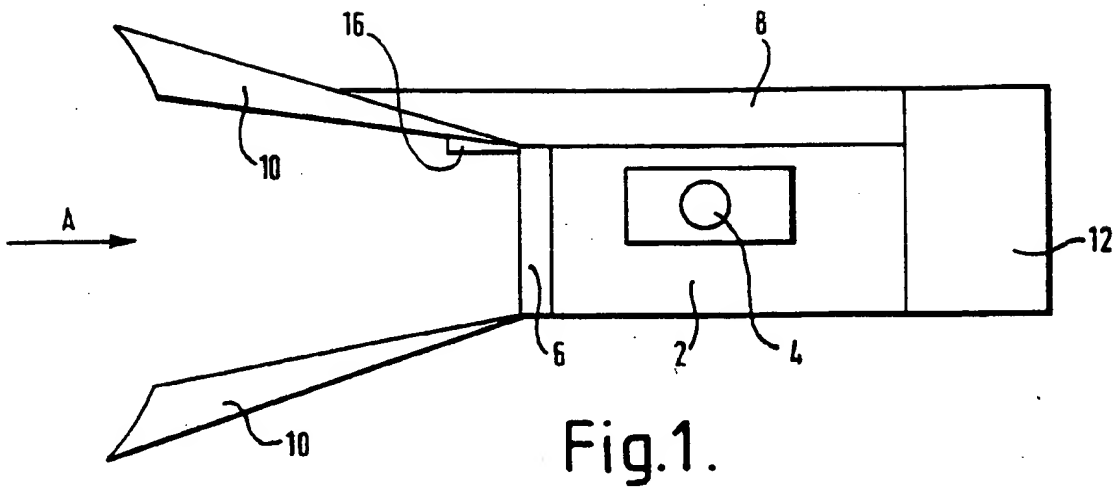

Fig.1.

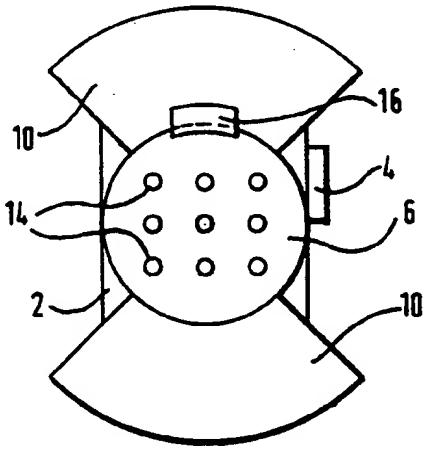

Fig.2.

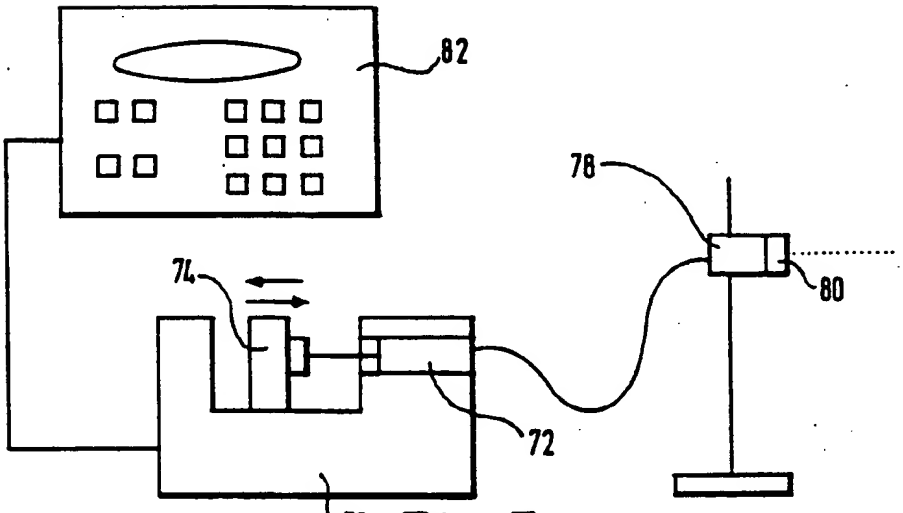

Fig.7.

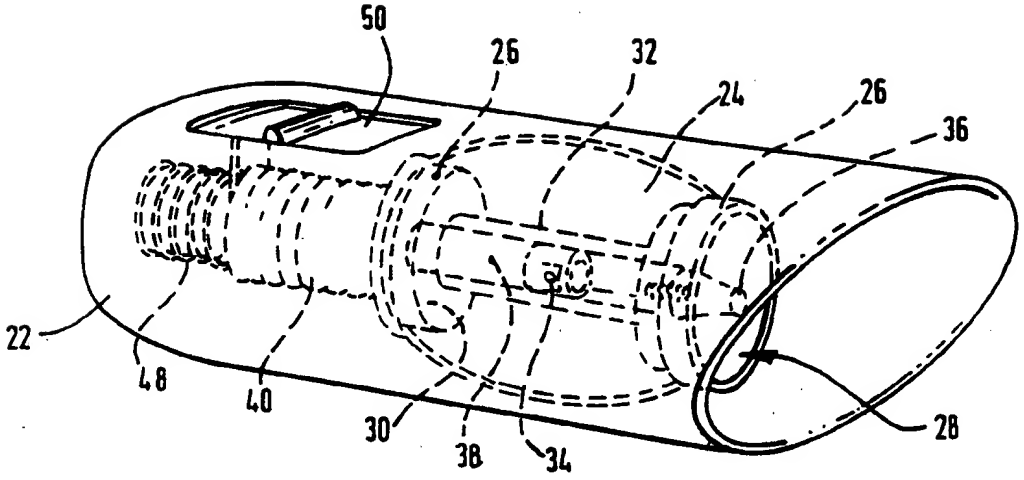

Fig.3.

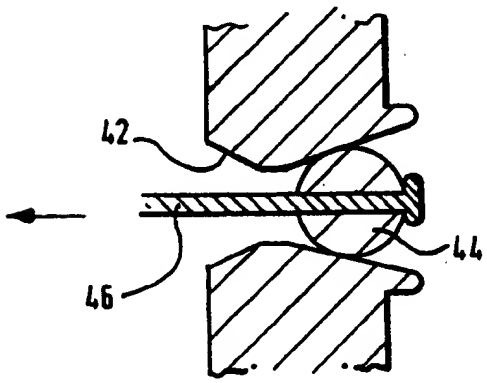

Fig.4.

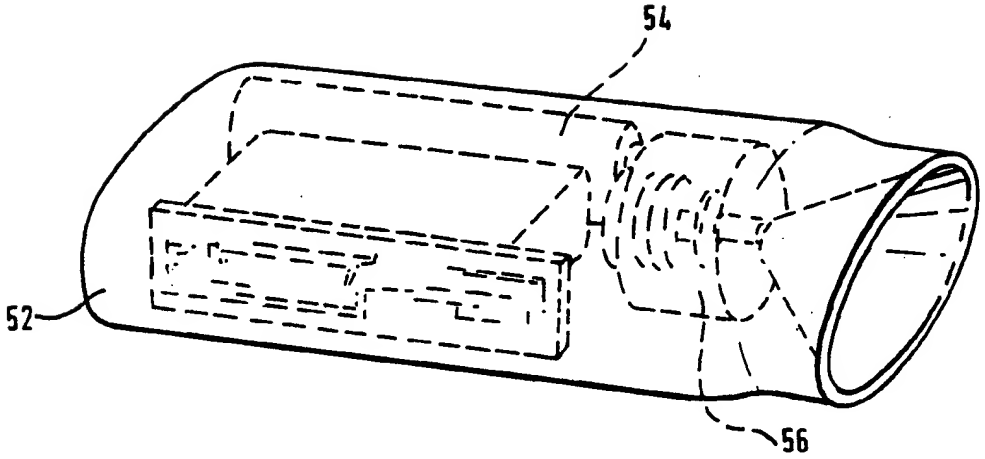

Fig.5.

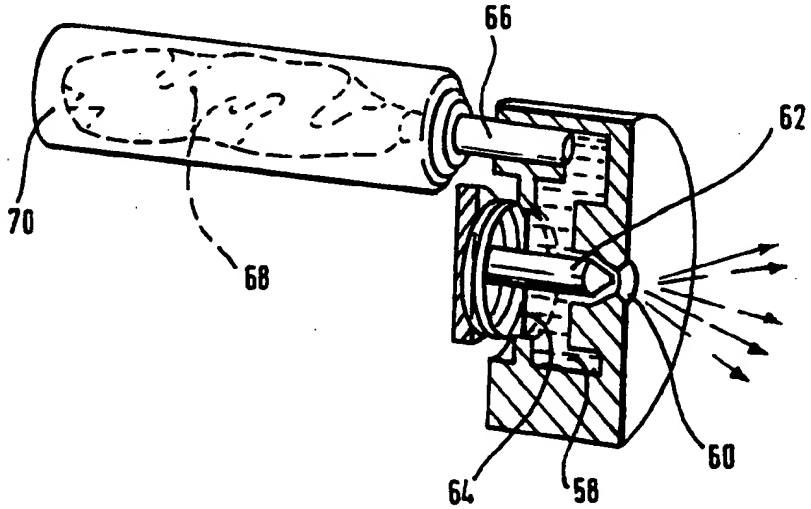

Fig.6.

INTERNATIONAL SEARCH REPORT

Int. .onal Application No
PCT/GB 95/01482

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61F9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61F B67D B65D B05B A61M F16K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US,A,5 152 435 (M. STAND ET AL.) 6 October 1992 see column 5, line 53 - column 7, line 7; figures	1-3
X	WO,A,94 03135 (THE SCHEPENS EYE RESEARCH INSTITUTE) 17 February 1994	1-3
Y	see claims 1,6,25,26; figures see page 11, line 8 - line 14	4-11
Y	EP,A,0 488 701 (PACESETTER INFUSION LTD) 3 June 1992 see abstract	4
Y	US,A,4 640 493 (H. DUDZIK) 3 February 1987 see abstract; figures	5-11

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 October 1995	13. 10. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Wolf, C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int. .onal Application No
PCT/GB 95/01482

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US,A,3 934 585 (D.M. MAURICE) 27 January 1976 see column 7, line 34 - column 8, line 56; figure 9 see abstract see column 8, line 57 - column 9, line 54; figures 10,11	6-11
A	US,A,5 012 496 (R.N. WEINREB ET AL.) 30 April 1991 see abstract; figure 11	2
A	US,A,5 171 306 (V.T. VO) 15 December 1992 see abstract	1-3
A	EP,A,0 224 352 (IMPERIAL CHEMICAL INDUSTRIES) 3 June 1987 cited in the application see abstract	1-3

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

national application No.
PCT/GB95/01482

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 12-17
because they relate to subject matter not required to be searched by this Authority, namely:
See Rule 39.1(IV) PCT

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. onal Application No
PCT/GB 95/01482

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A-5152435	06-10-92	NONE		
WO-A-9403135	17-02-94	US-A-	5368582	29-11-94
		AU-B-	5002493	03-03-94
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		DE-A-	2139653	17-02-72
		FR-A-	2104125	14-04-72
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		US-A-	5152424	06-10-92
US-A-5171306	15-12-92	NONE		
EP-A-0224352	03-06-87	AU-B-	600684	23-08-90
		AU-B-	6453486	21-05-87
		CA-A-	1296629	03-03-92
		JP-A-	62142110	25-06-87
		US-A-	4952212	28-08-90
		US-A-	5053000	01-10-91